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Transcranial Doppler: preventing stroke during carotid endarterectomy

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Carotid endarterectomy (CEA) is more effective at preventing strokes than medical therapy alone in those patients with severe symptomatic stenosis of the internal carotid artery and this benefit persists despite a perioperative stroke/death rate of approximately 5%. Thromboembolism has been established as the underlying cause of the majority of perioperative strokes, but this could not be detected using the existing methods of monitoring or quality control. Early studies demonstrated that transcranial Doppler monitoring (TCD) could detect intraoperative embolism, but the clinical significance of this finding was questioned as the incidence of these emboli far exceeded the incidence of perioperative strokes. This study aimed to establish the clinical relevance of TCD-detected emboli during CEA by differentiating emboli into two broad categories; air and particulate, and comparing the quantity of each with a variety of clinical outcomes including neurological and cognitive function, retinal fundoscopy, automated visual fields and CT/MRI brain scans. This prospective study was performed on 100 consecutive patients undergoing CEA with all assessments performed pre- and postoperatively by independent specialists in the relevant fields. Embolisation was detected in 92% of successfully monitored operations. Most emboli were characteristic of air microbubbles and not associated with the development of adverse clinical events. However, emboli characteristic of particulate material were detected during the initial dissection phase and in the recovery phase after final restoration of flow. These particulate emboli were associated with the development of both neurological and cognitive deficits. In particular, persistent embolisation after final restoration of flow heralded incipient carotid artery thrombosis and the development of stroke. Early intervention based on the TCD evidence of continuing embolisation can prevent the stroke from occurring.

Stroke is the third highest cause of death and the single most common cause of physical disability in the UK *(1)*. Each year 130 000 people in the UK suffer a stroke, causing severe mental and physical handicap and imposing a considerable burden of care on both the patient's family and society *(1)*. The economic burden of stroke is enormous and rapidly escalating, costing an estimated $15.9 to $20.6billion annually in the USA and £5billion annually in the UK *(2,3)*.

Intervention to prevent stroke is possible in approximately 10% of patients who experience transient ischaemic attacks (TIA) in the weeks or months before a major stroke resulting from significant (>70%) stenosis of the internal carotid artery *(4)*. In these patients, both the temporary and permanent neurological deficits are caused by embolisation from an unstable atherosclerotic plaque at the carotid bifurcation which can be removed by the operation carotid endarterectomy, thus preventing the expected stroke. Although it is customary to describe the severity of plaque in terms of the degree of stenosis, this is an indirect term which merely reflects the likelihood of a greater volume of plaque to embolise rather than any direct haemodynamic effect. Carotid endarterectomy (CEA) is unique in that it is one of the few surgical procedures proven to be effective by two international multicentre, randomised, controlled trials *(4,5)*. CEA is more effective at preventing stroke than medical therapy alone, despite the fact that up to 5% of patients may suffer a stroke as a result of the procedure *(4,5)*. This study aimed to investigate the aetiology of these perioperative strokes with a view to developing strategies to prevent them and improve the safety of the operation.

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Complications of carotid endarterectomy

Several large studies investigated the mechanisms causing perioperative strokes and deaths, and over 40 different mechanisms were identified (Table I, Table II) *(6–8)*. However, these individual mechanisms can be divided into three main groups: thromboembolic, haemodynamic and miscellaneous. Of these groups, thromboembolic causes were responsible for approximately 80% of strokes, while haemodynamic causes were responsible for only 20%.

Monitoring and quality control

In general, the strategies that have developed to attempt to prevent these strokes can be divided in to monitoring or quality control methods. Monitoring involves applying a method throughout the duration of the procedure which can detect when something is going wrong and provide an opportunity to put it right. Monitoring methods used during CEA include performing the operation under local anaesthesia, measuring internal carotid artery (ICA) stump pressure, electroencephalography (EEG), measuring somatosensory evoked potentials (SSEP), transcerebral oximetery, cerebral blood flow measurement and transcranial Doppler (TCD) monitoring *(9–15)*. Quality control assumes that the majority of complications are associated with technical errors which, if detected and corrected at the end of the operation, will prevent complications developing. The quality control methods applied during CEA include angiography, continuous wave Doppler, B-mode ultrasound, duplex/colour duplex ultrasound and angioscopy *(16–21)*. However, all these studies of monitoring or quality control techniques appear to demonstrate that the incidence of detected abnormalities by any technique (30%), far exceeds the morbidity/mortality rate for the operation (5%). This does not mean that these abnormalities are not clinically important, postmortem studies confirm that they are, but rather that there are multiple factors which determine whether or not a particular abnormality will result in a neurological deficit. Clinically important abnormalities are those that result in either a critical reduction in cerebral blood supply, thromboembolism, or both. In general, these factors cannot be predicted with 100% certainty using quality control methods, and therefore it is safest to correct all detected abnormalities.

With the exception of transcranial Doppler, the monitoring methods described above are primarily designed to detect haemodynamic abnormalities, which are responsible for only 20% of neurological deficits. They can not detect thromboembolic complications, which are responsible for 80% of neurological deficits, and therefore the application of these methods is unlikely to reduce the overall morbidity/mortality of the operation *(22)*.

Transcranial Doppler (TCD) monitoring offered the potential advantage of being able to detect both haemodynamic and thromboembolic complications occurring during the operation and in the immediate postoperative period when the complications of undetected technical errors occur *(23)*.

Table I. Causes of stroke in the perioperative period of carotid endarterectomy

Embolism	*Thrombosis*
Carotid dissection	Perioperative hypotension
Opening of shunt	Perishunt thrombosis
During shunting	Immediate postoperative carotid thrombosis
Restoration of ECA flow	Hypoplastic internal carotid artery
Restoration of ICA flow	Delayed postoperative thrombosis
Endarterectomy site embolus	
Aortic arch embolus	*Haemodynamic*
Cardiac embolus	Bradycardia
Cerebral angiography	Carotid clamping
Synchronous cardiac surgery	Shunt malfunction
	Shunt-induced spasm
Miscellaneous causes	Intracranial stenotic or occlusive disease
Strokes in other vascular territories	Occlusion of contralateral ICA
Carotid cavernous sinus fistula	Intracranial haemorrhage
Patch angioplasty rupture	Incomplete circle of Willis
Suture disruption with cervical haemorrhage	Hypotension
Wound infection with cervical haemorrhage	
Global anoxia; premature extubation	
Myocardial infarction	

Table II. Technical errors identified as resulting in perioperative morbidity/mortality

Technical error	
Embolism during operation	*Thrombus formation*
Air embolism	Idiopathic
Particulate embolism	Heparin dependent
Intimal flaps	Wall irregularity
Clamp induced	Intimal flap
Residual	Perishunt thrombosis
Shunt induced	
Incomplete endarterectomy	*Haemodynamic errors*
Suture stenosis	Carotid clamping
Distal arteriotomy closure	Shunt occlusion or kinking
Toe of patch angioplasty	Shunt malfunction
Uncorrected ICA kink	Shunt-induced arterial spasm
Intracranial haemorrhage	Intracranial stenosis/thrombosis
Hyperperfusion	
Intracranial aneurysm	

Transcranial Doppler

Transcranial Doppler is an ultrasound method which utilises the thin area of bone in the temporal region of the skull to insonate the middle cerebral artery (MCA), which can be considered the main blood supply to the motor and sensory cortex and the direct continuation of the internal carotid artery within the skull *(23)*.

TCD was first introduced to detect haemodynamic abnormalities, but TCD measures the velocity of blood, which is an indicator and not an absolute measure of blood flow *(24)*. However, in the clinical situation this 'indication' of blood flow is accurate enough and a MCA velocity of <10–15 cm/s during carotid clamping has been associated with flattening of the EEG. Alternatively, MCA velocity can be expressed as a percentage. Halsey found that a fall in the MCA velocity to less than 40% of its preclamp value caused mild cerebral ischaemia and $<15\%$ caused severe ischaemia *(24,25)*.

TCD detection of emboli

When emboli were first detected by TCD monitoring during CEA, they were assumed to be harmless air microbubbles *(26)*. Studies by Naylor *et al. (27)* and Jansen *et al. (28)* identified that emboli could be detected during most phases of CEA and in the majority of operations, but no association could be demonstrated between the incidence of TCD-detected emboli and the development of postoperative neurological deficits. The first evidence that TCD-detected emboli could be clinically important was provided by Spencer *et al. (15)* who detected embolic signals during the initial dissection phase of carotid endarterectomy before the arteriotomy. These signals were unlikely to be air emboli because the arterial system had not been breached and exhibited different signal characteristics.

Ultrasound is reflected from the interface between two substances, the bigger the difference in the composition of the substances the more ultrasound is reflected. The large difference between air and blood means that air reflects over 99% of incident ultrasound waves and that air emboli produce very strong signals which commonly overload the ultrasound receiver, producing visible artefact on the display of the TCD waveform. Particulate emboli, such as platelet aggregates, are very similar to the composition of blood and therefore produce weaker reflected signals which do not produce overload artefact and, unless the TCD machine is specifically set up to detect them, they are easily missed *(29)*. The emboli detected during the dissection phase were characteristic of particulate emboli, but Spencer *et al. (15)* also described the detection of particulate emboli in the immediate postoperative phase in two patients who subsequently developed neurological deficits. In one of these patients, the artery was re-explored the day after CEA and after a stroke had occurred and thrombus was found to have accumulated on the endarterectomy site.

However, these studies had not set out to specifically distinguish between air and particulate emboli or relate the occurrence of these emboli to clinical outcome and, therefore, the clinical relevance of TCD-detected emboli during CEA remained uncertain.

Clinical relevance of TCD-detected emboli during carotid endarterectomy

In order to investigate the clinical relevance of TCD-detected emboli, we undertook a prospective study of 100 consecutive patients undergoing carotid endarterectomy. The aims of the study were:

1 To accurately quantify and characterise emboli during carotid endarterectomy.
2 To detect all possible consequences of perioperative embolisation by the following pre- and postoperative investigations:
   (a) CT and MRI brain scans;
   (b) Retinal fundoscopy and 120-point Humphrey visual field analysis;
   (c) Neurological examination;
   (d) Psychometric testing.

All investigations were performed by independent specialists in the relevant field who were blind to the embolic status of the patients *(30)*.

Methods

Carotid endarterectomy

Carotid endarterectomy was performed under normotensive, normocarbic isofluorane anaesthesia using a standard method consisting of systemic heparinisation, routine shunting of all patients (Pruitt–Inahara), tacking proximal and distal intimal flaps, vein or Dacron® patch angioplasty and completion angioscopy quality control. Heparinisation was not routinely reversed. Before final clamp release and restoration of flow and after back venting and flushing procedures, the lumen of the artery was inspected by insertion of an angioscope to detect any residual luminal thrombus or intimal flaps *(31)*.

Transcranial Doppler monitoring

Continuous TCD monitoring of the ipsilateral middle cerebral artery was performed throughout each operation using a SciMed PcDop 842 TCD (SciMed, Bristol, UK). Preoperatively, each patient underwent a thorough interrogation of the circle of Willis and branches to determine the optimum insonation parameters for the middle cerebral artery. Intraoperatively, these parameters were reproduced and the probe was secured in place with an elastic headband protected by a semicircular headguard attached to the operating table. All signals were continuously recorded on to digital audio tape for postoperative playback and analysis. For the purposes of

evaluation the operation was divided into the following seven stages: dissection (skin preparation to carotid clamping); shunt opening (carotid clamping to 30 s after re-establishment of blood flow); shunt phase (30 s after shunt opening to immediately before restoration of blood flow through the external carotid artery (ECA); external carotid artery blood flow (restoration of external carotid artery flow to immediately before the restoration of internal carotid artery (ICA) blood flow; internal carotid artery blood flow (first 30 s of internal carotid artery blood flow); manipulation after carotid endarterectomy (30 s after restoration of flow to the cessation of procedures such as applying pressure to bleeding points or insertion of extra sutures); and recovery (termination of manipulation to the end of recording, approximately 30 min after final restoration of flow). The number of emboli detected by TCD during each stage was recorded and embolisation classified as predominantly air or particulate *(30)*.

Automated visual field testing and retinal fundoscopy

The visual fields of both eyes were tested independently on the automated Humphrey Field Analyser using a full-field 120-point screening test; a three zone strategy was used and each patient was given a score for points seen out of 120 for each eye. Absolute defects were awarded no score and relative defects scored half a point.

After completing the visual field test, the patient's fundi were examined under induced pupillary dilatation. Abnormalities of the fundi were recorded as were the visual acuity with pin-hole correction; the ophthalmologist's assessment of the history of amaurosis fugax; the presence of corneal opacities and the intraocular pressure measured in each eye.

The pre- and postoperative findings were compared for the eye ipsilateral and contralateral to the operated artery. Medians of visual field scores were calculated for the ipsilateral and contralateral eye both pre- and post-operatively. Deterioration in ipsilateral eye scores, independent of contralateral deterioration, was considered to be significant and related to episodes of intraoperative TCD-detected embolisation.

Computerised tomogram (CT) and magnetic resonance imaging (MRI) brain scans

CT and MRI brain scans were performed 1–4 days preoperatively and between the 5th and 7th day post-operatively, obtaining 12 transcranial slices. MRI brain scans were obtained using T_1, T_2 weighted images on a Siemans Magneton® (1 Tesla) magnetic resonance imaging scanner (Siemens, Germany).

Patient identification and the date of the scan were obscured and replaced with a study number and the letter 'A' and 'B' which were randomly assigned to preoperative and postoperative scans. All preoperative and post-operative pathological changes were recorded and new lesions correlated to embolic events during the operation.

Neurology and psychometric testing

A detailed neurological and cognitive assessment was performed 1–2 days before the operation and repeated 5–7 days after the operation when the patient was fully alert, mobile and off all analgesics. In addition, a basic neurological examination was performed in the recovery room immediately after surgery in order to detect any transient deficits. Muscle power was assessed using the MRC grading and each patient was assessed according to the National Institute of Health (NIH) Stroke Scale and the Rankin Disability Scale (RDS) *(32,33)*.

Cognitive function was assessed by the same independent neurologists using a 30-point assessment, including tests of orientation, recognition, instant recall, delayed recall, long-term recall, calculation, sentence construction and visuospatial skills. In addition, a further assessment was performed using a selection of Wechsler cognitive function tests, consisting of Wechsler orientation A and B (WOA & WOB), Wechsler concentration (WC), logical memory (WLM), paired association (WPA), and digit span (WDS) *(34,35)*.

Cognitive function tests were scored according to the recognised standards *(34,35)*. For the Wechsler logical memory, paired association and digit span, Form 1 was used preoperatively and Form 2 postoperatively to minimise practice effects. Intrasubject change between test scores before and after operation has been found to provide the best measure of the effects of operation on cognitive function *(36)*. The means and standard deviations for each test carried out before operation were obtained by use of the scores of the entire sample for that test. A patient was considered to show significant deterioration on a particular test if his score deteriorated more than one standard deviation below his score before the operation *(37)*.

Data analysis

Means and medians were obtained using the CIA statistics programme *(38)*. The non-parametric data were compared using medians obtained by the Wilcoxon method and expressed with 95% confidence intervals. New postoperative findings in the neurology, brain scans, eye tests and cognitive function tests were related to the incidence and character of TCD-detected emboli.

Results

Patient data

The patients recruited were consecutive patients admitted to Leicester Royal Infirmary for carotid endarterectomy between June 1992 and February 1994 and who consented to the study (100% compliance). All patients had severe (>70%) symptomatic carotid stenosis affecting the ipsilateral artery. The characteristics of the patients used in this study are summarised in Table III and compared with patients in the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid

Table III. Comparison of baseline characteristics of Leicester patients with patients in the NASCET and ECST

	Leicester	*ECST*	*NASCET*
Age	67 (median) 66 (mean)	62.2 (mean)	65 (median)
Sex ratio M:F	68:32	70:30	68:32
TIAs (+Am F) %	47 (65)	(78)	68
Stroke (+silent CT infarct) %	31 (52)	(50)	33
Previous MI %	19	27	18
Angina %	19	—	22
Peripheral vascular disease %	36	19	15
Diabetic %	14	9	17
Hypertension %	60	—	60
Current smokers (ex) %	18 (58)	56	37
Contralateral carotid occlusion %	21	—	6
Contralateral carotid stenosis 70–99%	16		8
Ipsilateral stenosis 70–79%	26		40
80–89%	42		38
90–99%	32		22

Am F = amaurosis fugax, CT = computerised tomogram, MI = myocardial infarct

Endarterectomy Trial (NASCET). Overall, the Leicester patients were at higher risk for CEA, being older and having a greater incidence of severe contralateral carotid stenosis and occlusion.

TCD monitoring

Successful intraoperative TCD monitoring was achieved in 91% of operations. Reasons for unsuccessful monitoring were hyperostosis (6%) and equipment failure (3%). Embolisation was detected in 92% of successfully monitored operations and the median number of emboli per operation was 39 (95% CI, 29–48.5; $K = 1598$). The number, duration and predominant character of emboli for each stage are summarised in Table IV.

The predominant character of the emboli during the dissection phase were particulate, while on opening the shunt the character of the emboli was predominantly air and quickly cleared. Similarly, the predominant character of emboli during shunting was air and precipitated by handling of the shunt or malfunction of the shunt allowing air to enter the arterial system. However, during shunting, two patients experienced gross air embolisation, associated with unrecognised puncture of the distal retaining balloon of the Pruitt–Inahara shunt and attempts at re-inflation.

Embolisation during restoration of ECA flow was predominantly characteristic of air, as were emboli detected in 83 (91%) of patients on restoration of flow through the ICA. Air emboli were also detected during the manipulation phase precipitated by the suturing of bleeding points.

During the recovery phase, embolisation was detected in six patients, which was predominantly characteristic of particulate. Two patients had only five and seven emboli, respectively, which ceased spontaneously. A further patient experienced 44 particulate episodes over a 40 min period after clamp release, but once again these stopped spontaneously. However, three patients in this group experienced severe, persistent particulate embolisation which in each case was associated with incipient carotid thrombosis and was terminated by re-operation and removal of the thrombus. The diagnosis was based on the detection of persistent particulate embolisation and in each patient the first emboli were detected within 9 min of restoration of blood flow through the ICA. In two patients, persistent embolisation was associated with a corresponding fall in MCA velocity as the ICA gradually occluded. In the remaining patient, the MCA velocity remained constant and diagnosis was based on the detection of persistent embolisation alone and the significance confirmed by the development of a contralateral upper limb weakness. In each case, platelet thrombus was found to have formed on the endarterectomy surface itself in the absence of any apparent technical defect. The thrombus was removed and a heparin infusion started which prevented further thrombus formation. The neurological consequences of this particulate embolisation are discussed below.

Table IV. Number, duration and character of TCD-detected emboli during carotid endarterectomy

Operative stage	*Number of patients (%)*	*Median number of emboli (95% CI)*	*Median duration of emboli (s) (95% CI)*	*Character of emboli*
Operation	91	30 (25–40)	2.65 (2.1–3.4)	
Dissection	23 (25%)	8 (4–14)	0.5 (0.225–0.8)	Particulate
Shunt open	71 (78%)	5.5 (4–7)	0.325 (0.225–0.5)	Air
Shunting	48 (53%)	6 (4–9.5)	0.3 (0.2–0.6)	Air
ECA flow	48 (52%)	9 (6–13)	0.65 (0.4–1.0)	Air
ICA flow	83 (91%)	10.5 (9–13)	0.925 (0.6–1.325)	Air
Manipulation	45 (49%)	14.5 (9.5–23.5)	1.05 (0.625–1.5)	Air
Recovery	6 (6.6%)	176 (5–672)	8.82 (0.25–33.6)	Particulate

Haemodynamic data

In order to minimise the effect of haemodynamic factors an intraluminal shunt was inserted in all but three patients. Technical difficulties prevented insertion in these three patients. However, in order to confirm that haemodynamic factors had been minimised the MCA velocity was recorded continuously throughout the operation. On clamping the carotid artery, the MCA velocity of 13 patients fell below 40% of the preclamp value indicating a mild risk of ischaemia, but only three patients had MCA velocity below 15% indicating a severe risk of ischaemia *(25)*. However, because of routine shunting, the mean time of ischaemia was only 2.2 min and once shunting had started no patient had a MCA velocity in the risk of ischaemia category.

Major neurological deficits: association with intraoperative embolisation

Four patients were detected with identifiable neurological deficits in the immediate postoperative period, and all four patients experienced significant episodes of intraoperative embolisation identified by TCD monitoring. Two permanent deficits and one temporary deficit were associated with gross particulate embolisation detected during the recovery phase. The remaining temporary deficit was associated with an episode of gross air embolisation due to shunt malfunction occurring in a susceptible patient with a pre-existing hemiparesis.

Patient 53 experienced 672 particulate emboli during the recovery phase, but before reversal of anaesthesia, associated with thrombosis of the endarterectomised artery and the development of a permanent right arm monoplegia, right leg monoparesis and expressive dysphasia (NIH = 11; RDS = 4).

Patient 98 experienced 157 particulate emboli during 1 h 50 min of the recovery phase monitored by TCD. Neurological examinations performed every 10 min after the end of the operation were normal until the 1 h 50 min stage when the patient started to develop a right arm monoparesis. The patient was returned to theatre and a large but non-occluding mass of thrombus was removed from the carotid bifurcation. The patient recovered well but a monoparesis confined to the right hand persisted (NIH = 1, RDS = 2).

Patient 99 experienced 348 particulate emboli during the recovery phase. This time the patient was returned to theatre immediately and a non-occluding mass of thrombus was removed from the carotid bifurcation. Postoperatively, a slight weakness of the right hand was demonstrated; however, this had completely resolved by 24 h with no residual deficit (NIH = 1, RDS = 1).

Patient 22 experienced 215 air emboli and 22 s duration of air embolisation when the distal retaining balloon of the intraluminal shunt was accidentally punctured by a misplaced suture needle. This patient, who had a pre-existing hemiparesis from a previous stroke before the operation experienced a slight worsening of his hemiparesis which had resolved by the 3rd postoperative day (NIH = 1–2; RDS = 2–3). Another patient without any pre-existing neurological deficit experienced air emboli (254 emboli, 14.2 s duration) by the same mechanism, but no neurological deficit could be detected in the postoperative period. In each of these patients an excess amount of embolisation was associated with the episodes described above, compared with the rest of the operation (Fig. 1). The majority of patients experienced embolisation at the time of restoration of flow through an intraluminal shunt and at final restoration of flow through the ICA; however, there was no neurological deficit associated with embolisation at these stages. Conversely, embolisation in the recovery phase was uncommon but associated with the development of neurological deficits. In particular, persistent embolisation in the recovery phase resulting in > 100 emboli, was always associated with the development of major neurological deficits.

Comparison of air embolisation and particulate embolisation and neurological deficit

Separate analysis of the association of neurological deficits with air or particulate embolisation provides a more conclusive indication of the clinical significance of intraoperative embolisation. Nine patients experienced > 100 episodes of air embolisation, but only one patient developed a temporary neurological deficit and this resolved completely within 2 days. In contrast, three patients experienced > 100 particulate emboli during the recovery period associated with carotid artery thrombosis and all developed neurological deficits (two permanent, one temporary).

Although the numbers of patients are small, these results provide evidence for a strong association between gross particulate embolisation during the recovery phase and the development of neurological deficits. Air embolisation during CEA would appear to be clinically less significant.

Cognitive function assessment

Cognitive function data were obtained for 94/100 patients. Preoperative testing was missed in four cases and postoperative testing in two. Out of 94 patients tested, 37 patients had a significant decrease in psychometric scores in one or more psychometric tests. Of the 37 patients who experienced a deterioration in postoperative cognitive function, 26 deteriorated in one test, six patients deteriorated in two, one patient deteriorated in three and four patients deteriorated in four or more.

There was a trend, but no statistically significant association between the number of intraoperative emboli and deterioration in cognitive function. The median number of embolic episodes experienced by patients demonstrating a fall in postoperative cognitive function scores was 52 (95% CI 35.5–100, $K = 171$). The median number of emboli for those patients with no deterioration was 32.5 (95% CI 24–44, $K = 537$). The difference between the medians was 12 (95% CI −2.0–34, $K = 681$).

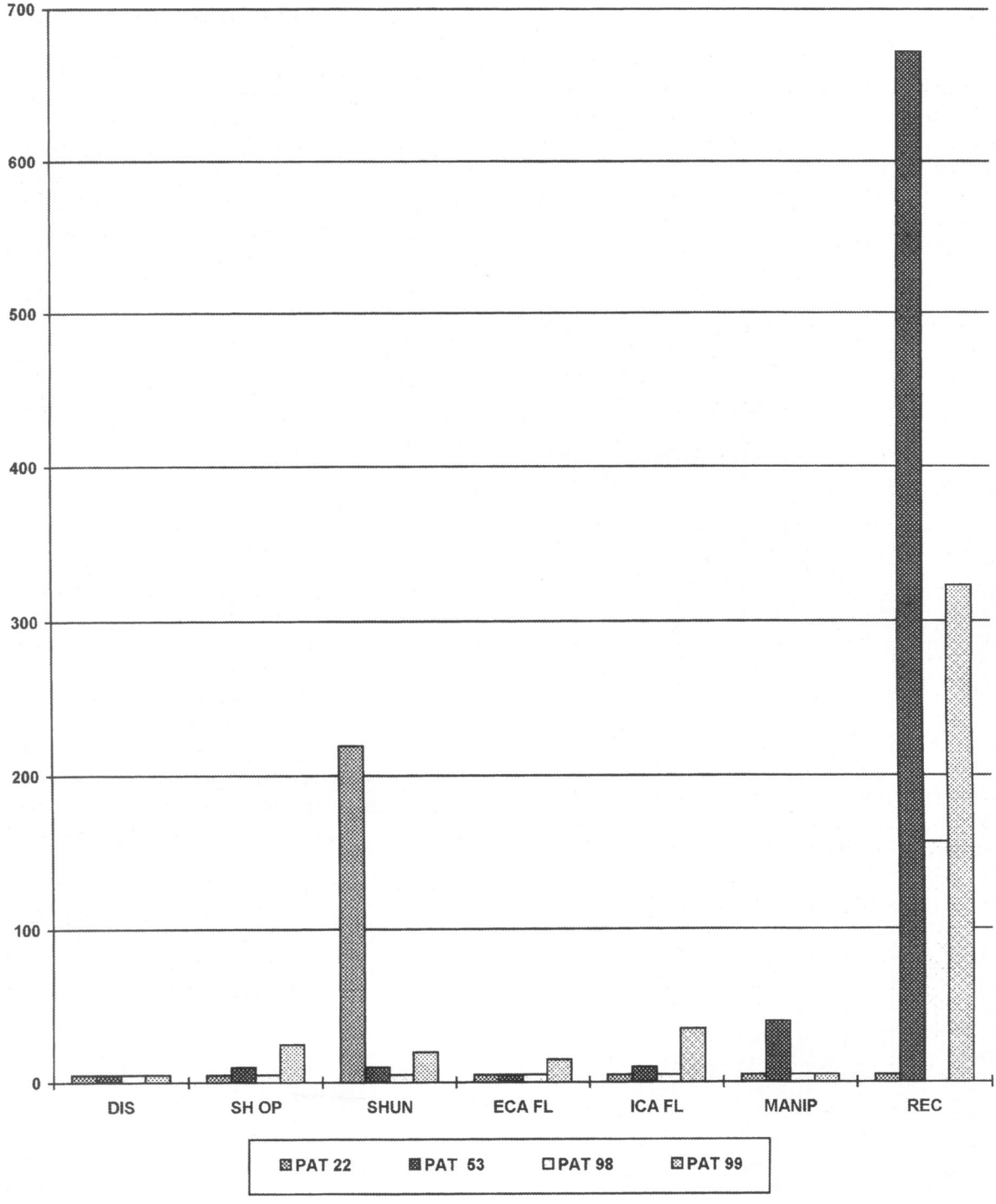

Figure 1. Relative number of emboli experienced at each operative stage by the four patients exhibiting postoperative neurological deficits.

Comparison of air and particulate emboli associated with cognitive deficit

There was no statistically significant difference in the number of air emboli experienced between those patients with a deterioration of cognitive function (median = 40, 95% CI 28–60, $K = 171$) and those without (median = 31, 95% CI 22.5–40.5, $K = 537$). Difference between the medians was 4 (95% CI −7.0–21, $K = 681$).

However, there was a statistically significant difference between the number of particulate emboli experienced by those suffering a postoperative deterioration in cognitive function and those who did not. Excluding gross embolisation in the recovery phase, the median number of particulate emboli experienced by those patients with no deterioration in cognitive function was 4.5 (95% CI 3.5–6.5, $K = 26$). The median number of particulate emboli in patients experiencing a deterioration in cognitive function was 14.8 (95% CI 7.5–23, $K = 11$). The difference between the medians was statistically significant (median = 11, 95% CI 1–20, $K = 45$). Similarly, there was a statistically significant difference between the duration of particulate embolisation.

Within those patients with cognitive deficit, there is a strong trend for greater cognitive deficit to be associated with greater number and duration of particulate embolisation. The median number of particulate emboli in patients deteriorating in one test was 0 (95% CI 0–3, $K=74$), while the median number of particulate emboli in patients deteriorating in two or more tests was 24.5 (95% CI 0–337.5, $K=11$). The difference between the medians was 14 (95% CI 0–42, $K=75$; 99% CI 0–157, $K=58$).

Preoperative retinal fundoscopy

Complete pre- and postoperative examinations were obtained in 91 patients. A convincing history of amaurosis fugax was obtained from 42 patients and, of these, five had evidence of embolisation on fundoscopy. A further six patients had fundoscopic evidence of embolisation but no symptoms attributable to amaurosis fugax, ie silent retinal emboli.

Postoperative retinal fundoscopy

Postoperatively, only one patient had evidence of new embolisation. This consisted of two small emboli affecting the periphery of the retina and this was not associated with a deterioration in visual field scores. One further patient had evidence of an intraoperative embolus, but this was in the contralateral eye and therefore was not considered in the analysis. Interestingly, this patient did have significant carotid disease in the contralateral artery (>90% stenosis).

The retinal fundoscopy study did not yield sufficient endpoints to merit correlation with episodes of intraoperative embolisation.

Visual field scores

Pre- and postoperative tests were obtained for 91 patients. There was no statistically significant difference in the median scores for the ipsilateral eye preoperatively (median=110, 95% CI 107–112.5, Wilcoxon $K=1598$) or postoperatively (median=109, CI 105–111.5, Wilcoxon $K=1598$) for the sample as a whole. The difference between the medians was 0.25 (95% CI −0.75–1.75, $K=1561$).

Similarly, there was no difference in the contralateral eye between preoperative scores (median=112, 95% CI 108.5–114, $K=1598$). and postoperative scores (median=112, 95% CI 108.75–114, $K=1598$). The difference between the medians was 0.25 (95% CI −1–0.5, $K=1561$). Interestingly, there was no difference between the medians of the ipsilateral and contralateral eyes preoperatively −1.0 (95% CI −2.25–0.25, $K=1598$), but postoperatively the small deteriorisation in the ipsilateral eye was sufficient to result in a significant difference between ipsilateral and contralateral eye scores at the 95% CI level (median= −1.5, 95% CI −3–0.5, $K=1598$). The possible causes for this will be discussed later.

Postoperative visual field scores

A postoperative deterioration in visual field score in the eye ipsilateral to the operated artery but not in the contralateral eye was considered to be significant. Thirty-four patients had a postoperative deterioration in their ipsilateral eye score, 40 improved their ipsilateral score and 17 remained the same. Eleven patients had a deterioration in ipsilateral eye scores but with no deterioration in the contralateral eye, the median deterioration was 2.75 (95% CI 1–4.75, $K=11$). Similarly, 11 patients had a postoperative deterioration in the contralateral eye without deterioration in the ipsilateral eye. The median deterioration was 1.38 (95% CI 0.75–3.75, $K=11$). Although there was a trend for deterioration to be greater in the ipsilateral eyes there was no statistically significant difference (median difference =0.5, 95% CI −0.5–3, $K=31$). In addition, none of these cases had fundoscopic evidence of embolisation and none had experienced episodes of gross intraoperative embolisation detected by TCD.

Preoperative CT brain scans

Complete sets of pre- and postoperative scans were obtained in 93/100 patients. Evidence of preoperative infarction in the hemisphere ipsilateral to the operated side was present in 39 patients and evidence of contralateral infarction was present in 22. Six patients had evidence of infarction in the contralateral hemisphere only and 11 patients had evidence of watershed infarction. Twenty patients had evidence of silent cerebral infarction on the ipsilateral side, of which 11 patients presented with a history of TIAs; six presented with a history of amaurosis fugax and three presented with a history of both.

Postoperative CT brain scans

New postoperative infarcts were detected in only three patients. These were patients 53, 98 and 99, who had all experienced gross particulate embolisation in the recovery phase associated with incipient carotid artery thrombosis. All new infarcts were in the parietal region within the territory of the MCA and their appearance was consistent with embolisation.

MRI brain scans

Complete sets of pre- and postoperative scans were obtained in 46/50 patients. There were no new infarcts identified by MRI scanning compared with CT scanning either preoperatively or postoperatively.

Discussion

The purpose of this study was to determine the clinical relevance of TCD-detached emboli and to achieve this it was necessary firstly to accurately quantify and characterise all intraoperative emboli and secondly to detect all possible clinical consequences of these emboli. To a large extent these aims have been achieved, and as a result of this study the clinical significance of TCD-detected emboli during CEA is much better understood. In this respect the negative findings of the study are as important

as the positive. Of particular importance is the fact that all significant neurological deficits were associated with major episodes of intraoperative embolisation detected by TCD. The absence of silent postoperative, cerebral infarction on either CT or MRI brain scans confirmed that no significant clinical episode had been missed.

The majority of patients experienced emboli at the time of restoration of blood flow through a shunt or at the end of the operation. Emboli occurring at these stages were predominantly characteristic of air and were not associated with the development of postoperative neurological deficits. Emboli occurring during the dissection and recovery stages were less common but characteristic of particulate emboli and it was embolisation during these stages that was associated with the development of both neurological and intellectual deficits.

Strokes occurring during the dissection phase were reported before the advent of TCD monitoring, but this was previously thought to be owing to the dislodgement of one large embolus *(6)*. Although, theoretically this can occur, this study would suggest that multiple embolisation is the more likely mechanism. Early detection of this embolisation provides a warning to the surgeon to modify the surgical approach to prevent further emboli which could result in a stroke.

Significant numbers of emboli during the recovery phase were only detected in three patients, but embolisation was associated with both incipient thrombosis of the operated artery and the development of major neurological deficits. Before TCD monitoring, methods to detect this serious complication depended on regular neurological observations in the recovery room. However, by the time neurological signs appeared permanent neurological damage had already occurred.

Postoperative analysis of the TCD recordings from the three cases of early carotid thrombosis revealed that the first particulate emboli were detected 6–9 min after final restoration of flow, but before a regular pattern of emboli was established. Intervention in the acute phase, based on the TCD detection of emboli had not previously been described; therefore, in the first two cases, the clinical significance of the emboli was not immediately appreciated and intervention was delayed, resulting in two minor strokes. However, in the final case, immediate intervention to remove the thrombus, based on the TCD evidence of persistent particulate embolisation and our experience of the previous two cases, prevented a permanent neurological deficit. These cases provided important evidence for the direct role of platelet emboli in the development of neurological deficits, since in none of the cases did MCA velocities fall to levels known to be associated with the risk of haemodynamic strokes.

The cause of thrombus formation remains unclear. Completion angioscopy excluded the presence of thrombus before restoration of flow and at reoperation no technical error was associated with the site of thrombus formation. Correction of the defect consisted of removal of the thrombus, a heparin infusion and restoration of blood flow. Haematological studies performed in the last two patients did not detect hypercoagulability or abnormal platelet function. However, even in the absence of an underlying cause, TCD monitoring in the postoperative phase offers the potential for early detection and correction of this complication before permanent neurological deficits occur.

There was no consistent relationship between the number of emboli and a deterioration in cognitive function. In particular, there was no association between the amount of air embolisation detected and a decrease in cognitive scores or the development of neurological deficits. However, a deterioration in cognitive function was associated with excess particulate embolisation during the dissection phase. This association achieved statistical significance, although caution must be expressed, since the possibility exists that potentially significant particulate embolisation occurred during other stages of the operation but was not detected, because the subtle particulate emboli signals were masked by the signal artefact associated with air emboli occurring at the same time.

The results of the eye tests did not show any clinically relevant retinal embolisation occurring as a result of carotid endarterectomy. Results from the preoperative tests suggest that for emboli to reduce significantly the visual field score in an eye the emboli need to be large and occlude a major retinal arterial branch, and this is an uncommon occurrence during CEA. However, CEA is associated with a small decrease in visual field scores in the ipsilateral eye, although no relationship could be demonstrated with the incidence of TCD-detected emboli. It may be that this small deterioration is caused by transient retinal emboli, which have been demonstrated to occur during coronary artery bypass using intraoperative retinal angiography *(39)*.

The evidence from this and other studies suggests that the clinical effect of TCD-detected embolisation is multifactorial and depends on the number, size and character of the emboli as well as patient susceptibility related to an inadequate collateral cerebral circulation and the presence of pre-existing cerebral infarcts *(24)*. The absolute differentiation of air and particulate emboli, and the sizing of emboli using TCD signal criteria alone is still the subject of much scientific study. Evidence has been produced that air and particulate emboli occurring during the same stage of the operation can be distinguished using a different form of spectral analysis known as Wigner, and this has been useful as a research tool in detecting particulate emboli during various stages of the operation *(40)*. At present, these results are only available after postoperative signal processing, and this limits its clinical application; however, it has confirmed the original assertions that emboli detected during the dissection and recovery phases are particulate. Therefore, for practical purposes, any emboli detected during dissection and recovery are potentially harmful, while emboli occurring during other operative phases are not, providing they do not occur in excessive amounts.

Recent prospective studies of postoperative embolisation have confirmed the initial findings of this study. Levi *et al. (41)* monitored 80 patients and identified eight patients who had >50 emboli in the first postoperative

hour. Of these eight patients, five then suffered a stroke. Bleeding complications associated with the use of heparin and occasional practical problems in returning a patient to theatre soon enough to be effective, prompted the investigation of an alternative approach to treat postoperative embolisation and prevent stroke. In a study by Lennard *et al. (42)* an incremental infusion of dextran-40 resulted in cessation of postoperative embolisation in the eight patients in whom it was used and no patient in this prospective study of 100 patients suffered a postoperative thromboembolic stroke. However, further experience suggests that, in the presence of an uncorrected technical error, dextran may be unable to arrest thrombus formation and reoperation is then indicated based on the TCD evidence of continued embolisation.

The results of these TCD studies combined with the estimates that embolisation is the causative factor in 80% of intraoperative strokes provides strong evidence that monitoring or quality control methods which are unable to detect embolisation are unlikely to reduce perioperative mortality and morbidity associated with CEA *(22)*. For any monitoring or quality control method to have an impact on perioperative morbidity/mortality, it must detect the majority of abnormalities while there is still time to correct the defect and prevent permanent damage. However, it is unlikely that one method could detect all the different abnormalities which have been established as a cause of stroke. An alternative approach is to monitor those factors necessary to the brain to ensure a successful outcome. By providing information on the adequacy of cerebral blood supply and the occurrence of particulate emboli, TCD monitors the two main pathways by which perioperative abnormalities cause strokes but, most importantly, provides this information soon enough to enable effective intervention.

In conclusion, this study has provided evidence of the clinical significance of TCD-detected embolisation during carotid endarterectomy. The majority of emboli are air and not associated with adverse clinical outcome. However, persistent particulate embolisation is associated with the development of neurological and intellectual deficits. In particular, this study has highlighted the role of TCD monitoring in providing an early warning of incipient carotid thrombosis in the immediate postoperative phase. Early intervention, based on TCD evidence, can reduce the morbidity and mortality associated with this serious complication.

This lecture was given to honour the memory of John Hunter, one of the most eminent surgeons and scientists of his age. When John Hunter collapsed and died during an acrimonious committee meeting at St George's Hospital, London, the post-mortem examination revealed significant cardiac disease as the probable cause of death. However, significant carotid artery disease was also discovered *(43)*. One might speculate that if John Hunter had been alive today, he may well have been referred to a vascular surgeon for a carotid endarterectomy. I am sure that any vascular surgeon in this position would wish to ensure that every means possible was employed to ensure a successful stroke-free outcome.

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